Research Proposal Form of the Thesis Entitled

A Retrospective Investigation in the Southern Telangana Population on "Plausible Role of ABO Blood Groups, Rh factor, and Serum Biomarkers in the Pathogenesis of COVID-19 Infection"

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INTRODUCTION

Covid sickness 2019 (Coronavirus) is a fresh out of the box new infirmity welcomed on by Coronavirus-2 that causes extreme intense respiratory condition (SARS-CoV-2).[1] Wuhan, China, became the principal known focal point of Coronavirus in December 2019. The WHO quickly designated the illness a pandemic that spread in waves over the world.[2, 3] COVID-19 transmissions happen mostly between people via respiratory droplets, coughing, sneezing, hand-shaking, and contact with an infected area. Aerosol and transmission by airborne modes are thought to be responsible for 10% to 30% of all colds that occur worldwide. Close contact increases the danger of lung problems, although they can still be inhaled over larger distances, especially indoors. Asymptomatic, pre-symptomatic, and symptomatic carriers can spread an infection.[6]

The human angiotensin changing over impetus 2 (ACE2) receptor, which emits an impression of being the essential area point and is imparted in the lung (basically type II alveolar cells) and the heart as well, causes SARS-CoV-2 infection. At the point when the renin-angiotensin framework is overactive, Angiotensin Changing over Chemical (ACE) - 2 receptors capability to lessen the impacts of angiotensin II.[4, 7, 8]

SARS-CoV-2 can take approximately 2 to 14 days to incubate. The clinical spectrum of COVID-19 includes asymptomatic patients, septic shock, and multiorgan failure. Fever, exhaustion, a dry cough, and diarrhoea are among the patients' most frequent symptoms.[4, 5]

Chest X-rays are the standard imaging procedure because the lungs are the principal organ involved. Additional methods for determining the nucleic acid of the COVID-19 virus include reverse transcription polymerase chain reaction (rRT-PCR), transcription-mediated amplification, and reverse transcription loop-mediated isothermal amplification (RT-LAMP) from a nasopharyngeal swab. Studies elicit that among the specific laboratory findings for COVID-19, there are elevated levels of Lactate dehydrogenase, Interleukin-6 (IL-6), D-Dimer, Alanine transaminase, C-reactive protein, Creatine kinase and Prothrombin time. The propensity for cytokine storm to lead to systemic inflammation is thought to be one feature of COVID-19.[4, 9, 10] The propensity of cytokine storm to induce systemic inflammation is thought to be a hallmark of COVID-19.

In many medical situations, CRP and D-Dimer levels are tested. Tillett and Francis were the first who in the 1930s identified, an acute phase reactant, CRP is a protein. It is a pentameric protein that the liver produces in response to the cytokine interleukin-6. Expanded CRP levels can be used as a good prognostic pointer for the vital diseases as well as demonstrating a supportive of fiery state.[11]

D-Dimers are a collection of peptide fragments created by the plasmin-mediated breakdown of crosslinked fibrin. D-dimers are a sign of crosslinked fibrin synthesis and breakdown, which reflects concurrent fibrinolysis and coagulation activities.[12] Since 2-3% of fibrinogen is changed over totally to fibrin and enters the fibrinolytic pathway under normal physiological conditions, it is distinguishable in unobtrusive sums in solid people. D-Dimer levels ascend because of any cycles that create or corrupt fibrin.[13] D-Dimer levels at the admission are higher than 2.0 g/mL (a fourfold rise) has been shown to be an accurate predictor of in-hospital death in patients with COVID-19.[14] The overactive immune response known as cytokine release syndrome (CRS) involves an excessive release of pro-inflammatory mediators. Acute respiratory distress syndrome is one clinical condition that is caused by this mechanism (ARDS).[15] Studies have shown that severe manifestations of COVID-19 are accompanied by a rapid increase in the biological levels of Interleukin-6, cytokines generated by activated macrophages majorly.[16] Because of the more subjects infected, it is essential to search for indicators that can assist us with assigning assets for these patients and be prepared ahead of time in light of the fact that our well-being frameworks are currently overburdened.[11]

A, B, and O, the three blood type alleles that are all encoded by the ABO gene, were discovered for the first time in 1901. These three alleles result in one of six genotypes and four phenotypes in red blood cells (RBCs), which determine the antigens on (RBCs) and the plasma antibodies. 17 ABO and Rh blood types have undergone the greatest research, testing, and clinical application among the 34 blood group types recognised by the International Society of Blood Transfusion (ISBT). Red blood cells and other organs express the oligosaccharides that make up the ABO blood group antigens (notably endothelium). The ABO blood type is determined by the antigenic structure on the surface of erythrocytes, whereas the Rh system determines.[18, 19]

Since its discovery, efforts have been made to examine any possible connections between the ABO blood type system and different diseases and infections. The ABO blood group's polymorphism has reportedly been linked to both the risk of developing and the results of a number of illnesses and infections, contaminations, including malignant growths, coronary illness, the hepatitis B infection, dengue hemorrhagic fever, Helicobacter pylori, etc.[20] Zhao et. al. were the first to depict what the Coronavirus defenselessness framework was meant for by the ABO blood type framework in affirmed Coronavirus cases at three unique emergency clinics in China.

As per arising proof, the ABO blood gathering might play a part in the immunopathogenesis of SARSCoV-2 disease, with blood group 'O' people having a lower chance of testing positive and blood group 'A' people having a higher weakness to contamination and a penchant for extreme illness.[22] Little observational investigations, broad affiliation examinations, and nationwide meta-relapse analysis have all been used to support a relationship between the ABO blood type and SARS-CoV-2/COVID-19 infection susceptibility and severity. Therefore, there is an imperative need to evaluate the connection amid Coronavirus disease and the ABO blood group framework.

Since, the current COVID-19 epidemic spread globally, there have been more than hundred million cases and two million deaths.[22,23] Healthcare and diagnostic resources are under tremendous strain due to the disease's fast spread. Knowing who most is at risk is essential to managing the pandemic because critically sick people are more liable to increment the epidemiological bend for Coronavirus and overtax the healthcare system. The likelihood of contracting an infection cannot yet be predicted by any biological biomarker.[24] Therefore, the care of Covid-19 patients urgently requires early and accurate clinical outcome indicators.

To elucidate the seriousness of Coronavirus disease, a few researchers investigated the association between the ABO and Rh blood groups and compared it to the relationship between laboratory indicators including CRP, IL-6, and D-Dimers. It is challenging to determine if the rise is big enough to be the source of the manifestations described in severe kinds since the majority of investigations to yet have been observational.

The goal of the current study is to analyse how these biomarkers and ABO blood groups affect the evaluation of the COVID-19 infection severity in the Southern Telangana region of India.

REVIEW OF LITERATURE

Cheng Y. et al (2005)[25] had anticipated the ABO blood type systems' ability to forecast Hong Kong's defenselessness to SARS-CoV contamination. It was shown that hospital staff members with blood group O were less likely to become ill than those with blood group non-O.

E.B. Milbrandt. et al (2009)[26] reported that elevated coagulation activity that was indicative of growing D-dimer levels was present in nearly 90% of inpatients with pneumonia.

W.H. Mahallawi. et al (2018)[16] showed that the most prevalent cytokine generated by activated macrophages, IL-6, elevated sharply in severe Corona virus symptoms.

S. Mahajan. et al (2019)[15] concluded that there is a link between cytokines in both MERS and SARS and severity of covid 19 diseases thereby, predicting a possible role of cytokines in covid 19 that could facilitate the invention of novel immunotherapies.

Rana R, Ranjan V, Kumar N (2019)[27] In contrast to O, AB, and Rh, which had a decreased probability of vulnerability to the diseases, the researchers found that A, B, and Rh+ were associated with the occurrence of Covid-19 in their study. Because of the predominance of an obscure part like comorbidity, it was likewise noticed that ABO or potentially Rh blood gatherings probably won't be a feasible lead for this connection.

Aljanobi GA, Alhajjaj AH, Alkhabbaz FL, Al-Jishi J (2020)[28] conducted a retrospective cohort study wherein association of the blood groups ABO in covid19 patients were studied. It was concluded that AB blood groups had an increased risk towards acquiring covid19 whereas O blood group had been observed to be protective.

N. Chen. et al (2020)[29] conducted a meta-analysis where six papers were examined and it was shown that the mean interleukin 6 concentration was 2.6 times greater in severe instances of cancer 19 as compared to patients with non-complicated disease.

Fang Liu. et al (2020)[30] concluded in their study that levels of IL-6 and CRP in serum could determine the severity and prognosis of Covid -19.

Tang, D. N, X. Li, Wang, Z. Sun (2020)[31] came to the conclusion that individuals with COVID-19 infection who had haemostatic problems and higher levels of D-dimer, a coagulation measure, in non-survivors had been compared to survivors. demonstrating their substantial relationship with one another. Additionally, he had found variations in biomarker levels, which led him to the conclusion that they would be relevant for developing a COVID-19 therapeutic intervention.

C. Qin, L. Zhou, Z. Hu (2020) [32] concluded that the levels of CRP had been strong factor to determine the occurrence and severity of covid 19 disease.

Ullah W. et.al (2020)[14] had found that levels of CR were a reliable indicator of both the prevalence and severity of covid infection. A high CRP (>101 mg/dl) on confirmation had anticipated a more prominent necessity for IMV and to a more elevated level of care, and on end of treatment, both a high CRP (>101 mg/dl) had been related with more prominent of chances of in clinic mortality. Moreover, those with CRP levels > 41.8 mg/L had a higher opportunity of advancing into an extreme type of Coronavirus infection.

L. Zhang. et al (2020)[33] conducted a retrospective cohort study wherein it was concluded that patients having higher D-dimer levels > 1.0 µg/mL had been proven to have great mortality amongst covid infected patients. Furthermore, it was seen that degrees of 2.0 µg/mL or more at the hour of affirmation had been the ideal end to anticipate in-emergency clinic mortality for Coronavirus. Subsequently, D-dimer could be an early and valuable indicative marker to work on the ideal administration of Coronavirus patients.

Massimo Franchini. et al (2021)[34] concluded in their study that O blood group had been protective towards Covid 19 infection as compared to non O blood groups. Furthermore, no link could be established between the o blood group and severity of disease.

Steven Lehrer, Peter H Rheinstein (2021)[35] in their study determined that ABO blood group had no correlation with the infection and outcome of Covid 19.

Liu N. et al (2021)[36] in their comprehensive review and meta analysis found that whereas O blood group is immune to the virus, the development of Covid 19 may be at risk for both A and B blood groups.

Singh P. et al (2021)[3] in their research concluded that AB Blood groups had a much more tendency to acquire Covid 19 whereas O blood group had the lowest susceptibility towards infection as compared to other blood groups.

Zhao J. et al (2021)[21] in their investigation, the researchers found that blood groups O had been protective and were therefore associated with a lower chance of infection, but blood groups ABO had a higher vulnerability to the occurrence of covid 19.

Salvador Domènech-Montoliu. et al (2023)[37] conducted a research in which it was observed that there had been a weak protection of O blood group and weak risk for susceptibility of other blood groups towards acquiring Covid 19 but results were observed to be non-significant.

AIM

To deduce a possible role of A, B, O Blood groups on the occurrence and the severity of COVID- 19 and to correlate with the rising common laboratory parameters (CRP, D-Dimers and IL-6).

OBJECTIVES

1) To research the connection between ABO blood gatherings and Coronavirus seriousness concerning defenselessness.

2) To ascertain how the Rh factor affects the disease's susceptibility and severity to COVID-19.

3) To ascertain how Covid -19 prognosis relates to ABO and Rh blood classes.

4) To identify the link among both ABO & Rh blood groups and the Covid-19 mortality rate & recovery rate.

5) To ascertain the relationship between the prognosis of COVID 19 infection and the age and gender groups.

6) To determine the role of IL-6, CRP & D-Dimers in the Covid 19 severity.

HYPOTHESIS

1. Generated hypothesis - The severity and susceptibility to infection of covid19 may be correlated with the RH factor, IL-6, CRP, and D-dimer levels, as well as the A, B, and O blood classes.

2. Null hyothesis - There is no discernible correlation between the severity of Covid-19 and susceptibility to infection and the A, B, and O blood types, the Rh factor, the levels of interleukin-6 (IL-6), CRP, and D-dimer.

METHODOLOGY

A cross sectional retrospective study will be done in private hospitals/laboratories in Southern Telangana. All the data will be collected retrospectively from patient databases including Age (between 20-60 years), Gender (male, females & transgender) who had signed Informed consent form. The patients' demographic parameters, ABO & Rh Blood group and the laboratory parameters including CRP, D-Dimers and IL-6 will be obtained from case record of patient database. Severity of covid 19 was assessed according to the classification. [38,39,40]

INCLUSION CRITERIA:

1) The gender groups in the range of 20 to 60 years would be included

2) The patients diagnosed with COVID -19 having a positive RT-PCR report.

3) The patients having blood group report of ABO & Rh Blood groups.

4) All the patients with the Laboratory results of CRP, D-Dimers and IL-6.

EXCLUSION CRITERIA:

1) The patients whose RT-PCR reports are not available or negative.

2) The patients whose complete data and records are not available.

3) Immunocompromised patients.

4) Patients diagnosed with other systemic diseases.

5) Patients on medication for Covid-19

6) Patients who had been showing recurrence or have been already Healed.

7) Patients on Steroids – drugs, immunomodulator drugs or other drugs for any systemic illness.

8) Patients out of the geographic limit of Telangana region were excluded.

SAMPLE SIZE CALCULATION:

Using the single proportion formula and the 50% COVID-19 prevalence, the result would be n = [Z /2] 2 P [1-P]/ d2 at 95% confidence level. where P = prevalence of 50% d = 5% of marginal error will be used, Z / 2 = 1.96, and 383 as sample size

STATISTICAL ANALYSIS:

Statistical values will be considered significant at p < 0.05. In order to assess the normality of distribution, Shapiro-Wilk test will be used. Data- mean ± standard Deviation, frequency and percentage. Student's t test will be used for independent samples. Chi- square test will be used to compare proportions. To study the odds of a blood type or antibody category testing positive, in a one-vs-all manner, Odds Ratio (OR) tests will be used and ORs will be reported to have a confidence interval of 95%.

RESULT/CONCLUSION EXPECTED

The results expected are as follows:

 There exists an established link between A, B and O blood groups and severity and susceptibility of covid19.

 A possible link between A, B and O blood groups and susceptibility of covid19.

 A significant relationship established between Rh factor and susceptibility of covid19.

 A possible role of various age and gender groups in prognosis of covid19.

 There is a possible association between IL-6, CRP & D-dimer levels and severity of covid19.

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